EXHIBIT A

US006254887B1

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Miller et al.

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(54) **CONTROLLED RELEASE TRAMADOL**

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(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(58) **Field of Search** 424/468, 470, 424/476, 480, 488, 494, 495, 498, 499, 502; 514/646

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(57) **ABSTRACT**

A controlled release preparation for oral administration contains tramadol, or a pharmaceutically acceptable salt thereof, as active ingredient.

33 Claims, 1 Drawing Sheet

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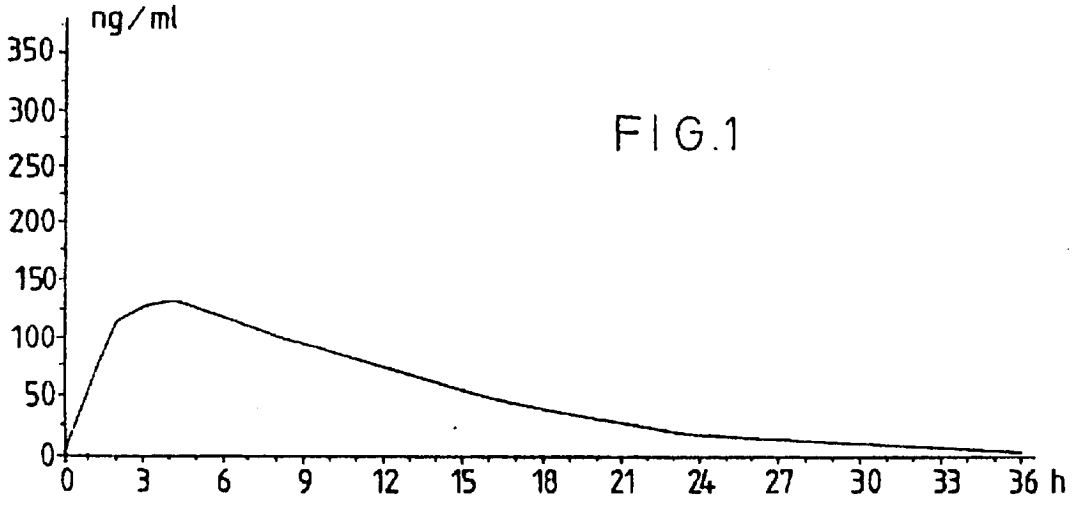
ng/ml
350
300
250
200
150
100
50
0
0
3
6
9
12
15
18
21
24
27
30
33
36 h

FIG.1

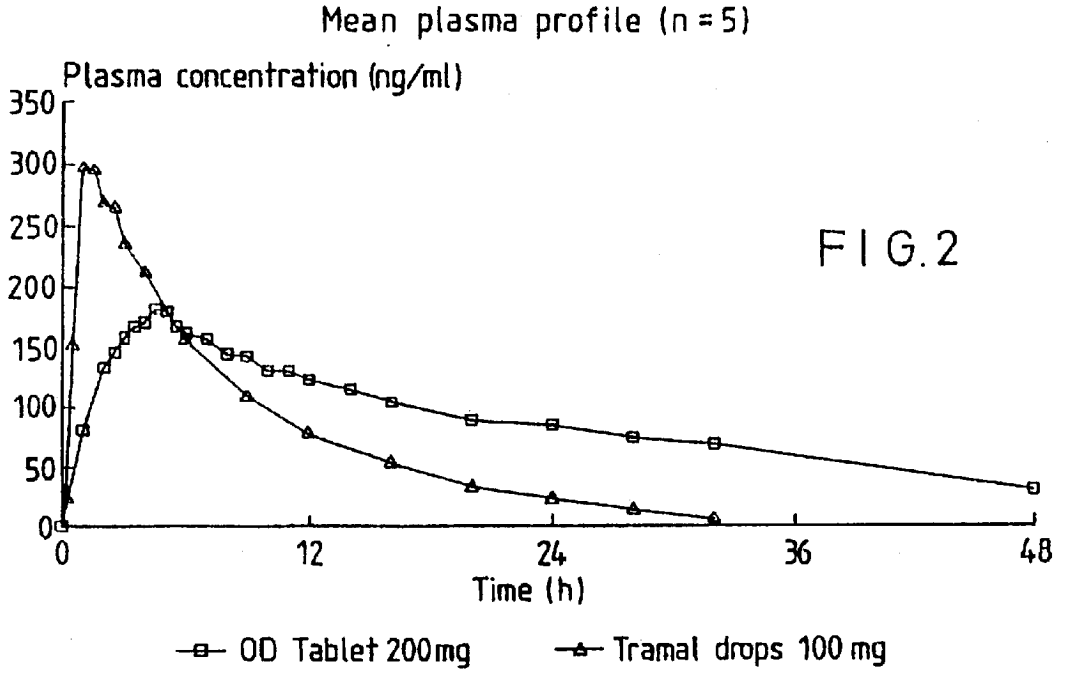
Mean plasma profile (n = 5)
Plasma concentration (ng/ml)
350
300
250
200
150
100
50
0
0
12
24
36
48
Time (h)
OD Tablet 200mg
Tramal drops 100 mg

FIG.2

CONTROLLED RELEASE TRAMADOL

This is a divisional of application Ser. No. 08/241,129, filed May 10, 1994 (now U.S. Pat. No. 5,591,452).

The present invention relates to a controlled release preparation for oral administration, to processes for its preparation and to its medical use. In particular, (lie invention relates to a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof.

Tramadol, which has the chemical name (+)-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol, is an orally active opioid analgesic. Conventional release preparations in the form of capsules, drops and suppositories containing tramadol, or more particularly its hydrochloride salt, have been commercially available for many years for use in the treatment of moderate to severe pain; Such preparations, however, do not provide a controlled release of the tramadol. Moreover, despite tramadol's long-standing use, controlled release preparations for oral administration containing tramadol as active ingredient have not even previously been described in the literature.

It is an object of the present invention to provide an oral controlled release tramadol preparation suitable for at least twelve-hourly (e.g. up to twenty-four hourly) administration for the treatment of pain.

The present invention therefore provides a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof for oral administration.

Suitable pharmaceutically acceptable salts of tramadol for use according to the present invention are those conventionally known in the art such as pharmaceutically acceptable acid addition salts. The hydrochloride salt is particularly preferred.

A controlled release preparation according to the present invention is one that achieves slow release of a drug over an extended period of time, thereby extending the duration of drug action over that achieved by conventional delivery. Preferably such a preparation maintains a drug concentration in the blood within the therapeutic range for 12 hours or more.

The present inventors have found that in order to allow for controlled release tramadol over at least a twelve hour period following oral administration, the in vitro release rate preferably corresponds to the following % rate of tramadol released:

TABLE 1

TIME (H)	% RELEASED
1	0–50
2	0–75
4	3–95
8	10–100
12	20–100
16	30–100
24	50–100
36	>80

Another preferred preparation especially suited for twice-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released:

TABLE 2

TIME (H)	% RELEASED
1	20–50
2	40–75

TABLE 2-continued

TIME (H)	% RELEASED
4	60–95
8	80–100
12	90–100

Yet another preferred preparation particularly suited for once-a-day dosing has an in-vitro release rate corresponding to the following % rate of tramadol released:

TABLE 3

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90

A still further preferred preparation in accordance with the invention also particularly suited for once-a-day dosing has an in vitro release rate corresponding to the following % rate if tramadol released.

TABLE 4

TIME (H)	% RELEASED
1	0–30
2	0–40
4	3–55
8	10–65
12	20–75
16	30–88
24	50–100
36	>80

More preferably a preparation for once-a-day dosing has an in vitro release rate substantially as follows:

TIME (H)	% TRAMADOL RELEASED
1	15–25
2	25–35
4	30–45
8	40–60
12	55–70
16	60–75

Another preferred dissolution rate in vitro upon release of the controlled release preparation for administration twice daily according to the invention, is between 5 and 50% (by weight) tramadol released after 1 hour, between 10 and 75% (by weight) tramadol released after 2 hours, between 20 and 95% (by weight) tramadol released after 4 hours, between 40 and 100% (by weight) tramadol released after 8 hours, more than 50% (by weight) tramadol released after 12 hours, more than 70% (by weight) released after 18 hours and more than 80% (by weight) tramadol released after 24 hours.

Furthermore, it is preferred in the case of a controlled release preparation for administration twice daily that after 8 hours following oral administration between 70 and 95% (by weight) tramadol is absorbed in vivo, between 77 and 97% (by weight) tramadol is absorbed after 10 hours and between 80 and 100% (by weight) tramadol is absorbed after 12 hours.

A formulation in accordance with the invention suitable for twice-a-day dosing may have a tmax of 1.5 to 8 hours, preferably 2 to 7 hours, and a W_{50} value in the range 7 to 16 hours.

A formulation in accordance with the invention suitable for once-a-day dosing may have a tmax in the range of 3 to 6 hours, preferably 4 to 5 hours and a W_{50} value in the range of 10 to 33 hours.

The W_{50} parameter defines the width of the plasma profile at 50% Cmax, i.e. the duration over which the plasma concentrations are equal to or greater than 50% of the peak concentration. The parameter is determined by linear interpolation of the observed data and represents the difference in time between the first (or only) upslope crossing the last (or only) downslope crossing in the plasma profile.

The in vitro release rates mentioned herein are, except where otherwise specified, those obtained by measurement using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm.

The in vitro absorption rate is determined from measurement of plasma concentration against time using the deconvolution technique. A conventional release tramadol drop preparation (Tramal (trade mark), Grunenthal) was used as the weighting-function and the elimination half life of tramadol was taken as 7.8 hours.

Tie controlled release preparation according to the invention preferably contains an analgesically effective amount of tramadol or a pharmaceutically acceptable salt thereof, conveniently in the range of from 50 to 800 mg, especially 100, 200, 300, 400 to 600 mg (calculated as tramadol hydrochloride) per dosage unit.

The controlled release preparation according to the invention may be presented, for example, as granules, spheroids, pellets, multiparticulates, capsules, tablets, sachets, controlled release suspensions, or in any other suitable dosage form incorporating such granules, spheroids, pellets or multiparticulates.

The active ingredient in the preparation according to the invention may suitably be incorporated in a matrix. This may be any matrix that affords controlled release tramadol over at least a twelve hour period and preferably that affords in-vitro dissolution rates and in vivo absorption rates of tramadol within the ranges specified above. Preferably the matrix is a controlled release matrix. Alternatively, normal release matrices having a coating which provides for controlled release of the active ingredient may be used.

Suitable materials for inclusion in a controlled release matrix include

(a) Hydrophillic or hydrophobic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially alkylcelluloses are preferred. The preparation may conveniently contain between 1% and 80% (by weight) of one or more hydrophillic or hydrophobic polymers.

(b) Digestible, long chain (C_8–C_{50}, especially C_{12}–C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, hydrocarbons having a melting point of between 25 and 90° C. are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The preparation may conveniently contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(c) Polyalkylene glycols. The preparation may suitably contain up to 60% (by weight) of one or more polyalkylene glycols.

One particularly suitable controlled release matrix comprises one or more alkylcelluloses and one or more C_{12}–C_{36} aliphatic alcohols. The alkylcellulose is preferably C_1–C_6 alkyl cellulose, especially ethyl cellulose. The controlled release preparation according to the invention preferably contains from 1 to 20% (by weight), especially from 2 to 15% (by weight) of one or more alkylcelluloses.

The aliphatic alcohol may conveniently be lauryl alcohol, myristyl alcohol or stearyl alcohol but is preferably cetyl alcohol or more preferably cetostearyl alcohol. The controlled release preparation suitably contains from 5 to 30% (by weight) of aliphatic alcohol, especially from 10 to 25% (by weight) of aliphatic alcohol.

Optionally the controlled release matrix may also contain other pharmaceutically acceptable ingredients which are conventional in the pharmaceutical art such as diluents, lubricants, binders, granulating aids, colourants, flavourants, surfactants, pH adjusters, anti-adherents and glidants, e.g. dibutyl sebacate, ammonium hydroxide, oleic acid and colloidal silica.

The controlled release preparation according to the invention may conveniently be film coated using any film coating material conventional in the pharmaceutical art. Preferably an aqueous film coating is used.

Alternatively, the controlled release preparation according to the invention may comprise a normal release matrix having a controlled release coating. Preferably the preparation comprises film coated spheroids containing the active ingredient and a spheronising agent.

The spheronising agent may be any suitable pharmaceutically acceptable material which may be spheronised together with the active ingredient to form spheroids. A preferred spheronising agent is microcrystalline cellulose. The microcrystalline cellulose used may suitably be, for example, Avicel PH 101 or Avicel PH 102 (Trade Marks, FMC Corporation).

Optionally the spheroids may contain other pharmaceutically acceptable ingredients conventional in the pharmaceutical art such as binders, bulking agents and colourants. Suitable binders include water soluble polymers, water soluble hydroxyalkyl celluloses such as hydroxypropylcellulose or water insoluble polymers (which may also contribute controlled release properties) such as acrylic polymers or copolymers for example ethylcellulose. Suitable bulking agents include lactose.

The spheroids are coated with a material which permits release of the active ingredient at a controlled rate in an aqueous medium. Suitable controlled release coating materials include water insoluble waxes and polymers such as polymethylacrylates (for example Eudragit polymers, Trade Mark) or water insoluble celluloses, particularly ethylcellulose. Optionally, water soluble polymers such as polyvinylpyrrolidone or water soluble celluloses such as hydroxypropylmethylcellulose or hydroxypropylcellulose may be included. Optionally other water soluble agents such as polysorbate 80 may be added.

Alternatively the drug may be coated onto inert nonpareil beads and the drug loaded beads coated with a material which permits control of the release of the active ingredient into the aqueous medium.

In a further aspect the present invention provides a process for preparing a controlled release preparation according to the present invention comprising incorporating tramadol or a pharmaceutically acceptable salt thereof in a controlled release matrix, for example by

(a) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof and one or more alkylcelluloses,

(b) mixing the alkylcellulose containing granules with one or more C_{12-36} aliphatic alcohols; and optionally

(c) shaping and compressing the granules, and film coating, if desired; or

(d) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof, lactose and one or more alkylcelluloses with one or more C_{12-36} aliphatic alcohol; and, optionally,

(e) shaping and compressing the granules, and film coating, if desired.

The controlled release preparation according to the invention may also be prepared in the form of film coated spheroids by

(a) granulating the mixture comprising tramadol or a pharmaceutically acceptable salt thereof and a spheronising agent;

(b) extruding the granulated mixture to give an extrudate;

(c) spheronising the extrudate until spheroids are formed; and

(d) coating the spheroids with a film coat.

One preferred form of unit dose form in accordance with the invention comprises a capsule filled with controlled release particles essentially comprising the active ingredient, a hydrophobic fusible carrier or diluent and optionally a hydrophillic release modifier. In particular, the controlled release particles are preferably prepared by a process which comprises forming a mixture of dry active ingredient and fusible release control materials followed by mechanically working the mixture in a high speed mixer with an energy input sufficient to melt or soften the fusible material whereby it forms particles with the active ingredient. The resultant particles, alter cooling, are suitably sieved to give particles having a size range from 0.1 to 3.0 mm, preferably 0.25 to 2.0 mm. An example according to the invention is described below which is suitable for the commercial production of dosage units.

When using such a processing technique it has been found that, in order most readily to achieve the desired release characteristics (both in vivo and in vitro as discussed above) the composition to be processed should comprises two essential ingredients namely:

(a) tramadol or salt thereof; and

(b) hydrophobic fusible carrier or diluent; optionally together with

(c) a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material.

We have found that the total amount of tramadol or pharmaceutically acceptable salt thereof in the composition may vary within wide limits, for example from 10 to 90% by weight thereof.

The hydrophobic fusible component (b) should be a hydrophobic material such as a natural or synthetic wax or oil, for example hydrogenated vegetable oil, hydrogenated castor oil, microcrystalline wax, Beeswax, Carnauba wax or glyceryl monostearate, and suitably has a melting point of from 35 to 140° C., preferably 45 to 110° C.

The release modifying component (c), when a water soluble fusible material, is conveniently a polyethylene glycol and, when a particulate material, is conveniently a pharmaceutically acceptable material such as dicalcium phosphate or lactose.

Another preferred process for the manufacture of a formulation in accordance with the invention comprises

(a) mechanically working in a high-speed mixer, a mixture of tramadol or a pharmaceutically acceptable salt in particulate form and a particulate, hydrophobic fusible carrier or diluent having a melting point from 35 to 140° C. and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates,

(b) breaking down the larger agglomerates to give controlled release seeds; and

(c) continuing mechanically working with optionally a further addition of low percentage of the carrier or diluent.

(d) optionally repeating steps (c) and possibly (b) one or more times.

This process is capable of giving a high yield (over 80%) of particles in a desired size range, with a desired uniformity of release rate of tramadol or salt thereof.

The resulting particles may be sieved to eliminate any over-or undersized material then formed into the desired dosage units by for example, encapsulation into hard gelatin capsules containing the required dose of the active substance or by compression into tablets.

In this method in accordance with the invention preferably all the tramadol or salt thereof is added in step (a) together with a major portion of the hydrophobic fusible release control material used. Preferably the amount of fusible release control material added in step (a) is between 10% and 90% w/w of the total amount of ingredients added in the entire manufacturing operation, more preferably between 20% and 70% w/w.

Stage (a) of the process may be carried out in conventional high speed mixers with a standard stainless steel interior, e.g. a Collette Vactron 75 or equivalent mixer. The mixture is processed until a bed temperature about 40° C. or above is achieved and the resulting mixture acquires a cohesive granular texture, with particle sizes ranging from about 1–3 mm to fine powder in the case of non-aggregated original material. Such material, in the case of the embodiments described below, has the appearance of agglomerates which upon cooling below 40° C. have structural integrity and resistance to crushing between the fingers. At this stage the agglomerates are of an irregular size, shape and appearance.

The agglomerates are preferably allowed to cool. The temperature to which it cools is not critical and a temperature in the range room temperature to 37° C. may be conveniently used.

The agglomerates are broken down by any suitable means, which will comminute oversize agglomerates and produce a mixture of powder and small particles preferably with a diameter under 2 mm. It is currently preferred to carry out the classification using a Jackson Crockatt granulator using a suitable sized mesh, or a Comil with an appropriate sized screen. We have found that if too small a mesh size is used in the aforementioned apparatus the agglomerates melting under the action of the beater or impeller will clog the mesh and prevent further throughput of mixture, thus reducing yield. A mesh size of 12 has been found adequate.

The classified material is returned to the high speed mixer and processing continued.

It is believed that this leads to cementation of the finer particles into particles of uniform size range.

In one preferred form of the method of the invention processing of the classified materials is continued, until the hydrophobic fusible materials used begin to soften/melt and optionally additional hydrophobic fusible material is then added. Mixing is continued until the mixture has been transformed into particles of the desired predetermined size range.

In order to ensure uniform energy input into the ingredients in the high speed mixer it is preferred to supply at least part of the energy by means of microwave energy.

Energy may also be delivered through oiler means such as by a heating jacket or via the mixer impeller and chopper blades.

After the particles have been formed they are cooled or allowed to cool, and may then be sieved to remove any over or undersized material.

The resulting particles may be used to prepare dosage units in accordance with the invention in the form of e.g. tablets or capsules in manners known per se.

We have also found that particles containing tramadol or a salt thereof produced by a melt processing as described in application PCT/SE93/00225 and the process described and claimed in our prior unpublished UK application No. 9324045.5 filed onNov. 23, 1993 as well as the process described herein are particularly useful for processing into the form of tablets.

We have found that by suitable selection of the materials used in forming the particles and in the tabletting and the proportions in which they are used, enables a significant degree of control in the ultimate dissolution and release rates of the tramadol or salt thereof from the compressed tablets.

Usually, to form a tablet in accordance with the invention, particles prepared as described above will be admixed with tabletting excipients e.g. one or more of the standard excipients such as diluents, lubricants, binding agents, flow aids, disintegrating agents, surface active agents or water soluble polymeric materials.

Suitable diluents are e.g. microcrystalline cellulose, lactose and dicalcium phosphate. Suitable lubricants are e.g. magnesium stearate and sodium stearyl fumarate. Suitable binding agents are e.g. hydroxypropyl methyl cellulose, polyvidone and methyl cellulose.

Suitable disintegrating agents are starch, sodium starch glycolate, crospovidone and croscarmalose sodium.

Suitable surface active are Poloxamer 188®, polysorbate 80 and sodium lauryl sulfate. Suitable flow aids are talc colloidal anhydrous silica. Suitable water soluble polymers are PEG with molecular weights in the range 1000 to 6000.

To produce tablets in accordance with the invention, particles produced in accordance with the invention may be mixed or blended with the desired excipient(s), if any, using conventional procedures, e.g. using a Y-Cone or bin-blender and the resulting mixture compressed according to conventional tabletting procedure using a suitable size tabletting mould. Tablets can be produced using conventional tabletting machines, and in the embodiments described below were produced on standard single punch F3 Manesty machine or Kilian RLE15 rotary tablet machine.

Generally speaking we find that even with such a highly water soluble active agent as tramadol or salt thereof tablets formed by compression according to standard methods give very low release rates of the active ingredient e.g. corresponding to release over a period of greater than 24 hours, say more than 36. We have found that the release profile can be adjusted in a number of ways. For instance a higher loading of the drug will be associated with increased release rates; the use of larger proportions of the water soluble fusible material in the particles or surface active agent in the tabletting formulation will also be associated with a higher release rate of the active ingredient. By controlling the relative amounts of these ingredients it is possible to adjust the release profile of the tramadol or salt thereof.

In order that the invention may be well understood the following examples are given by way of illustration only.

BRIEF DESCRIPTION OF DRAWINGS

The present invention is further illustrated in connection with the accompanying drawings in which:

FIG. **1** is a graphical depiction of the serum levels of tramadol following administration of one tablet according to Example 2 in 12 healthy volunteers: and

FIG. **2** is a graphical depiction of the plasma profile resulting from single dose administration of the tablet of Example 8 in comparison to the administration of a commercial preparation of tramadol drops 100 mg in a trial involving five healthy male volunteers.

EXAMPLE 1

Tablets having the following formulation wee prepared:

	mg/tablet
Tramadol Hydrochloride	100
Lactose Ph. Eur.	68.0
Ethylcellulose (Surelease ® 25% solids)	15
Purified Water Ph. Eur.	13.3*
Cetostearyl Alcohol Ph. Eur. (Dehydag wax 0)	42.00
Magnesium Stearate Ph. Eur.	2.00
Purified Talc Ph. Eur.	3.00
	230.00

*Removed during processing.

Tramadol hydrochloride (100 mg) and lactose (68 mg) were granulated, transferred to a fluid bed granulator and sprayed with ethylcellulose (15 mg) and water. The granules were then dried at 60° C. and passed through a 1 mm screen.

To the warmed tramadol containing granules was added molten cetostearyl alcohol (42 mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets.

The tablets were coated with a film coat having the formulation given below.

	mg/tablet
Hydropopylmethylcellulose Ph. Eur. 15 cps (Methocel E15)	0.770
Hydroxypropylmethylcellulose (Ph. Eur. 5 cps (Methocel E5)	3.87
Opaspray M-1-7111B (33% solids)	2.57
Polyethylene glycol 400 USNF	0.520
Purified Talc Ph. Eur.	0.270
Purified Water Ph. Eur.	55.52*

*Remove during processing.

EXAMPLE 2

Tablets having the following formulation were prepared:

	mg/tablet
Tramadol hydrochloride	100.0
Lactose Ph. Eur.	58.0
Ethylcellulose USNF	15.0

-continued

	mg/tablet
(Ethocel 45 CP)	
Cetostearyl alcohol Ph. Eur.	52.0
(Dehydag wax O)	
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

A mixture of tramadol hydrochloride (100 mg), lactose (58 mg) and ethylcellulose (15 mg) was granulated whilst adding molten cetostearyl alcohol (52 mg) and the whole was nixed thoroughly. The granules were allowed to cool and sieved through a 1.6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets which were coated with a film coat having the formulation given in Example 1.

EXAMPLE 3

Film coated tablets were produced following the procedure described in Example 2 and having the following formulation:

	mg/tablet
Tramadol hydrochloride	100.00
Lactose Ph. Eur.	70.50
Hydroxyethylcellulose Ph. Eur.	12.50
Cetostearyl alcohol Ph. Eur.	42.00
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

In vitro dissolution studies

In vitro dissolution studies were conducted on tablets prepared as described above. Results are given in Table 1.

TABLE 1

	WT % TRAMADOL RELEASED		
Time (h)	Example 1	Example 2*	Example 3
1	39	35	43
2	52	47	60
4	67	62	84
8	82	78	97
12	90	86	—

*Measured on tablet core

In a trial involving 12 healthy volunteers the serum levels of tramadol following administration of one tablet according to Example 2 was found to be as illustrated in FIG. **1**.

EXAMPLES 4 AND 5

Particles having the formulations given in Table II below were prepared by the steps of:

i. Placing the ingredients (a) and (c) (total batch weight 0.7 kg) in the bowl of a 10 liter capacity Collette Gral Mixer (or equivalent) equipped with variable speed mixing and granulating blades;

ii. Mixing the ingredients at about 150–1000 rpm whilst applying heat until the contents of the bowl are agglomerated.

iii. Classifying the agglomerated material by passage through a Comil and/or Jackson Crockatt to obtain controlled release seeds.

iv. Warming and mixing the classified material in the bowl of a 10 liter Collette Gral, until uniform multiparticulates of the desired pre-determined size range are formed in yield of greater than 80%. This takes approximately 5 minutes.

v. Discharging the multiparticulates from the mixer and sieving them to separate out the multiparticulates collected between 0.5 and 2 mm aperture sieves.

TABLE II

Example	4	5
(a) Tramadol HCl (Wt %)	50	75
(b) Hydrogenated Vegetable Oil (Wt %)	50	25

EXAMPLE 6

Samples of the particles from Example 4 were blended with magnesium stearate and purified talc using a Y-Cone or bin-blender. The blended mixture was then compressed using either (1) 14×6 mm, (2) 16×7 mm or (3) 18.6×7.5 mm capsule shaped tooling on a single punch F3 Manesty tabletting machine to give tablets giving 200, 300 and 400 mg of tramadol HCl. The ingredients per dosage unit amounted to the following:

TABLE III

TABLET	MG/TABLET		
INGREDIENT	1	2	3
Tramadol Hcl	200	300	400
Hydrogenated Vegetable Oil	200	300	400
Sub Total	400	600	800
Purified Talc	12.63	18.95	25.26
Magnesium Stearate	8.42	12.63	16.84

The tablets were assessed by the dissolution using Ph. Eur. Paddle Method 100 rpm, 0.1 N HCl.

To assess the non-compressed particles the Ph Eur. Paddle was replaced by a modified Ph Eur. Basket.

The results are shown in Table IV below;

TABLE IV

HOURS AFTER START OF TEST	Particles	Tablet 1	Tablet 2	Tablet 3
	% TRAMADOL HCl RELEASED			
1	54	16	15	15
2	68	23	20	21
3	76	28	25	25
4	82	32	28	28
6	89	40	35	35
8	93	46	41	40
10	96	50	45	45
12	98	55	49	49
16	100	63	57	56
20	NR	70	63	NR

These results confirm the effectiveness of the tabletting in reducing the release rate.

EXAMPLE 7

Samples of the particles from Example 5 were then tabletted using a procedure similar and the ingredients per unit dosage amounted to:

TABLE V

TABLET	MG/TABLET		
INGREDIENT	4	5	6
Tramadol Hcl	200	360	400
Hydrogenated Vegetable Oil	66.7	100	133
Sub Total	266.7	400	533
Purified Talc	7.63	11.44	15.25
Magnesium Stearate	5.16	7.63	10.17

The tablets and samples of non-compressed multiparticulates (each sample containing 400 mg of tramadol hydrochloride) were assessed by the dissolution method also described above. The results are shown in Table VI below;

TABLE VI

HOURS AFTER START OF TEST	Particles	Tablet 4	Tablet 5	Tablet 6
	% TRAMADOL HCl RELEASED			
1	77	43	40	42
2	92	64	55	56
3	98	75	65	66
4	100	83	72	73
6	102	94	83	84
8	102	100	91	91
10	102	NR	96	97

These results show that by increasing the loading of the highly water soluble tramadol hydrochloride (75% w/w in this example compared with 50% w/w in Example 6) a significantly faster release rate of the active ingredient can be achieved.

EXAMPLE 8

Example 4 was repeated but with (lie following formulation:

Tramadol HCl	200 mg/tablet
Hydrogenated Vegetable Oil	163.0 mg/tablet

The resulting multiparticulates were blended as described in Example 6 with the following;

Purified Talc	11.5 mg/tablet
Magnesium Stearate	7.66 mg/tablet

The blend was then compressed as described in Example 6 but using 15 mm×6.5 mm normal concave capsule shaped plain/plain punches.

The resulting tablets were then assessed by the dissolution method described above. The results are shown in Table V.

HOURS AFTER START OF TEST	% TRAMADOL HCl RELEASED
1	20
2	27
3	32
4	37
6	44
8	50
10	55
12	60
16	67
20	73
24	77

In a trial involving five healthy male volunteers the plasma profile resulting from single dose administrations of the above tablet are shown in FIG. **2** in comparison to the administration of a commercial preparation of Tramadol drops 100 mg.

What is claimed is:

1. A controlled release oral pharmaceutical preparation suitable for dosing every 24 hours comprising

a substrate comprising a pharmaceutically effective amount of tramadol or a salt thereof;

said substrate coated with a controlled release coating;

said preparation having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0,1 N hydrochloric acid at 37° C. and using UV detection at 270 nm, between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours; between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight, said preparation providing a therapeutic effect for about 24 hours after oral administration.

2. A controlled release preparation as claimed in claim **1**, having an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. And using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	20–50
2	40–75
4	60–95
8	80–100
12	90–100.

3. A controlled release preparation as claimed as claim **1**, having an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90.

4. A controlled release preparation as claimed in claim **1**, having an in vitro dissolution rate (measured by the Ph. Eur.

Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	0–30
2	0–45
4	3–55
8	10–65
12	20–75
16	30–88
24	50–100
36	>80.

5. A controlled release preparation according to claim **1**, wherein said substrate comprises a plurality of spheroids.

6. A controlled release preparation according to claim **5**, wherein said spheroids comprise a spheronizing agent.

7. A controlled release preparation suitable for dosing every twelve hours comprising

a substrate comprising an effective amount of tramadol or pharmaceutically acceptable salt thereof and said substrate coated wit a controlled release coating;

said preparation exhibiting an in vitro dissolution rate when measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm, such that between 5 and 50% (by weight) tramadol is released after 1 hour, between 10 and 75% by weight) tramadol is released after 2 hours, between 20 and 95% (by weight) tramadol is released after 4 hours, between 40 and 100% (by weight) tramadol is released after 8 hours, more than 50% (by weight) tramadol is released after 12 hours, more than 70% (by weight) tramadol is released after 18 hours and more than 80% (by weight) tramadol is released after 24 hours said preparation providing a therapeutic effect for at least about 12 hours after oral administration.

8. A controlled release preparation according to claim **7**, wherein said substrate comprises a plurality of spheroids.

9. A controlled release preparation according to claim **7** which provides a t_{max} at 2 to 7 hours after oral administration.

10. A controlled release preparation according to claim **7**, which provides a t_{max} at 1.5 to 8 hours after oral administration.

11. A controlled release preparation according to claim **7**, which provides a W_{50} from about 7 to about 16 hours after oral administration.

12. A controlled release preparation according to claim **7**, wherein said substrate is a tablet.

13. A controlled release oral pharmaceutical tablet suitable for dosing every 24 hours comprising

a tablet containing a pharmaceutically effective amount of tramadol or a salt thereof;

said tablet coated with a controlled release coating;

said coated tablet having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm, between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours; between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight, and providing a W_{50} in the range of 10 to 33 hours when orally administered, said coated tablet providing a therapeutic effect for about 24 hours after oral administration.

14. A controlled release oral pharmaceutical tablet suitable for dosing every 24 hours comprising

a tablet containing a pharmaceutically effective amount of tramadol or a salt thereof;

said tablet coated with a controlled release coating;

said coated tablet providing a therapeutic effect for about 24 hours after oral administration and having an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	20–50
2	40–75
4	60–95
8	80–100
12	90–100.

15. A controlled release oral pharmaceutical tablet in accordance with claim **15** which has

an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. using UV detection at 27 mm) as set forth below:

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90.

16. A controlled release preparation according to claim **1**, which when orally administered provides a W_{50} value in the range of 10 to 33 hours.

17. A controlled release preparation according to claim **1**, having an in vitro dissolution rate (measured by the Ph. Eur. Paddle method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 mm) as set forth below:

TIME (H)	% RELEASED
1	15–25
2	25–35
4	30–45
8	40–60
12	55–70
16	60–75.

18. A controlled release preparation according to claim **1**, which when orally administered provides a t_{max} at 4–5 hours after oral administration.

19. A controlled release oral pharmaceutical preparation suitable for dosing every 24 hours comprising

a substrate comprising a pharmaceutically effective amount of an opioid analgesic consisting essentially of tramadol or a salt thereof;

said substrate coated with a controlled release coating;

said preparation having a dissolution rate in vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm, between 0 and 50% tramadol released after 1 hour; between 0 and 75% tramadol released after 2 hours; between 3 and 95% tramadol released after 4 hours; between 10 and 100% tramadol released after 8 hours; between 20 and 100% tramadol released after 12 hours; between 30 and 100% tramadol released after 16 hours; between 50 and 100% tramadol released after 24 hours; and greater than 80% tramadol released after 36 hours, by weight, said preparation providing a therapeutic effect for about 24 hour, after oral administration.

20. A controlled release preparation according to claim **1**, wherein said substrate comprises inert non-pareil beads coated with said tramadol.

21. A controlled release preparation according to claim **7**, wherein said substrate comprises inert nonpareil beads coated with said tramadol.

22. A controlled release preparation according to claim **19**, wherein said substrate comprises inert non-pareil beads coated with said tramadol.

23. A controlled release preparation according to claim **19**, wherein said substrate is a tablet.

24. A controlled release preparation according to claim **19**, wherein said substrate comprises spheroids.

25. A controlled release preparation according to claim **19**, which provides a t_{max} from 3 to 6 hours after orally administered to a human patient,

26. A controlled release preparation according to claim **25**, which provides a W_{50} value in the range from 10 to 33 hours.

27. A controlled release preparation in accordance with claim **1**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

28. A controlled release preparation in accordance with claim **7**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

29. A controlled release preparation in accordance with claim **13**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

30. A controlled release preparation in accordance with claim **14**, wherein said controlled release coating comprises a material selected tom the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

31. A controlled release preparation in accordance with claim **19**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

32. A controlled release preparation in accordance with claim **26**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

33. A controlled release preparation in accordance with claim **11**, wherein said controlled release coating comprises a material selected from the group consisting of a water insoluble wax, a water insoluble polymer, a water insoluble cellulose and mixtures of any of the foregoing.

* * * * *

EXHIBIT B

US007074430B2

(12) United States Patent
Miller et al.

(10) Patent No.: US 7,074,430 B2
(45) Date of Patent: *Jul. 11, 2006

(54) **CONTROLLED RELEASE TRAMADOL TRAMADOL FORMULATION**

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This patent is subject to a terminal disclaimer.

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(58) **Field of Classification Search** 424/468, 424/470, 476, 480, 488, 444, 445, 498, 499, 424/502; 514/646
See application file for complete search history.

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(57) **ABSTRACT**

A controlled release preparation for oral administration contains tramadol, or a pharmaceutically acceptable salt thereof, as active ingredient.

17 Claims, 2 Drawing Sheets

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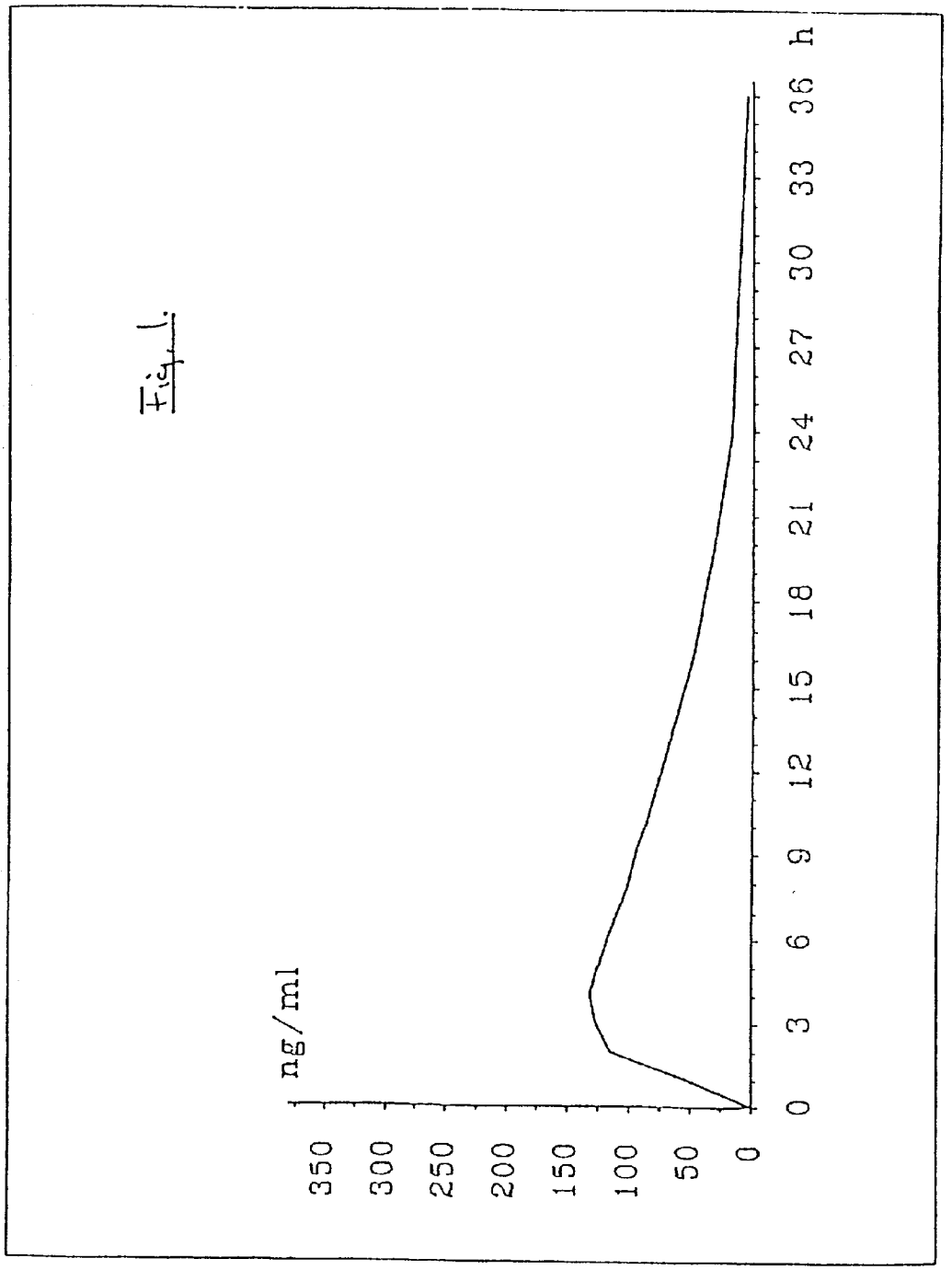
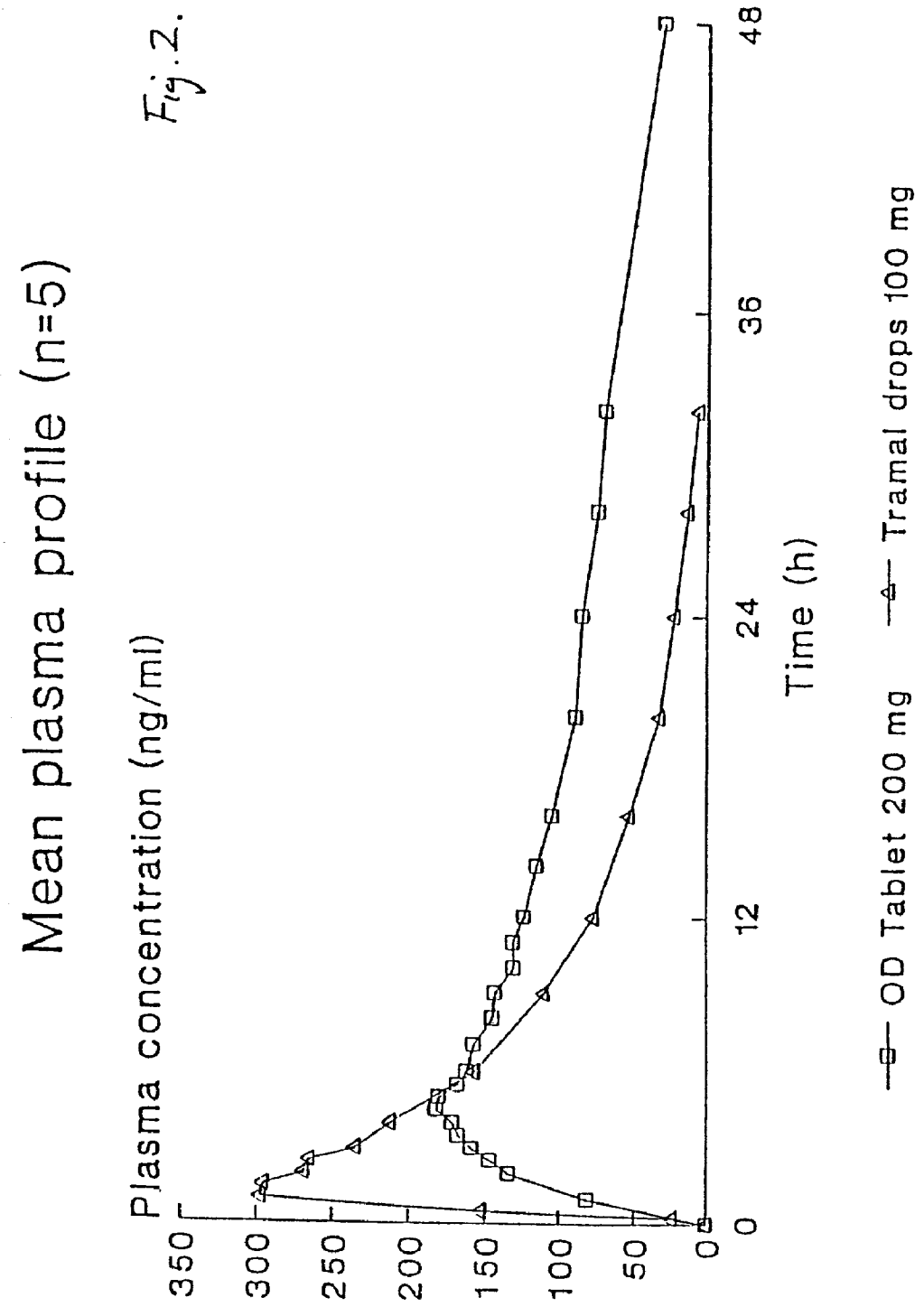


Fig. 1.

Fig. 2.


Mean plasma profile (n=5)
Plasma concentration (ng/ml)
350
300
250
200
150
100
50
0
0
12
24
36
48
Time (h)
OD Tablet 200 mg
Tramal drops 100 mg

CONTROLLED RELEASE TRAMADOL TRAMADOL FORMULATION

This application is a continuation of U.S. patent application Ser. No. 08/677,798, filed Jul. 10, 1996; now U.S. Pat. No. 6,254,887 which is a continuation of U.S. patent application Ser. No. 08/241,129, filed May 10, 1994 (now U.S. Pat. No. 5,591,452).

The present invention relates to a controlled release preparation for oral administration, to processes for its preparation and to its medical use. In particular, the invention relates to a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof.

Tramadol, which has the chemical name (±)-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol, is an orally active opioid analgesic. Conventional release preparations in the form of capsules, drops and suppositories containing tramadol, or more particularly its hydrochloride salt, have been commercially available for many years for use in the treatment of moderate to severe pain; Such preparations, however, do not provide a controlled release of the tramadol. Moreover, despite tramadol's long-standing use, controlled release preparations for oral administration containing tramadol as active ingredient have not even previously been described in the literature.

It is an object of the present invention to provide an oral controlled release tramadol preparation suitable for at least twelve-hourly (e.g. up to twenty-four hourly) administration for the treatment of pain.

The present invention therefore provides a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof for oral administration.

Suitable pharmaceutically acceptable salts of tramadol for use according to the present invention are those conventionally known in the art such as pharmaceutically acceptable acid addition salts. The hydrochloride salt is particularly preferred.

A controlled release preparation according to the present invention is one that achieves slow release of a drug over an extended period of time, thereby extending the duration of drug action over that achieved by conventional delivery. Preferably such a preparation maintains a drug concentration in the blood within the therapeutic range for 12 hours or more.

The present inventors have found that in order to allow for controlled release tramadol over at least a twelve hour-period following oral administration, the in vitro release rate preferably corresponds to the following % rate of tramadol released:

TABLE 1

TIME (H)	% RELEASED
1	0–50
2	0–75
4	3–95
8	10–100
12	20–100
16	30–100
24	50–100
36	>80

Another preferred preparation especially suited for twice-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released:

TABLE 2

TIME (H)	% RELEASED
1	20–50
2	40–75
4	60–95
8	80–100
12	90–100

Yet another preferred preparation particularly suited for once-a-day dosing has an in-vitro release rate corresponding to the following % rate of tramadol released:

TABLE 3

TIME (H)	% RELEASED
1	0–50
2	0–75
4	10–95
8	35–100
12	55–100
16	70–100
24	>90

A still further preferred preparation in accordance with the invention also particularly suited for once-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released.

TABLE 4

TIME (H)	% RELEASED
1	0–30
2	0–40
4	3–55
8	10–65
12	20–75
16	30–88
24	50–100
36	>80

More preferably a preparation for once-a-day dosing has an in vitro release rate substantially as follows:

TIME (H)	% TRAMADOL RELEASED
1	15–25
2	25–35
4	30–45
8	40–60
12	55–70
16	60–75

Another preferred dissolution rate in vitro upon release of the controlled release preparation twice daily according to the invention, is between 5 and 50% (by weight) tramadol released after 1 hour, between 10 and 75% (by weight) tramadol released after 2 hours, between 20 and 95% (by weight) tramadol released after 4 hours, between 40 and 100% (by weight) tramadol released after 8 hours, more than 50% (by weight) tramadol released after 12 hours, more than 70% (by weight) released after 18 hours and more than 80% (by weight) tramadol released after 24 hours.

Furthermore, it is preferred in the case of a controlled release preparation for administration twice daily that after 8 hours following oral administration between 70 and 95% (by weight) tramadol is absorbed in vivo, between 77 and

97% (by weight) tramadol is absorbed after 10 hours and between 80 and 100% (by weight) tramadol is absorbed after 12 hours.

A formulation in accordance with the invention suitable for twice-a-day dosing may have a tmax of 1.5 to 8 hours, preferably 2 to 7 hours, and a W_{50} value in the range 7 to 16 hours.

A formulation in accordance with the invention suitable for once-a-day dosing may have a tmax in the range of 3 to 6 hours, preferably 4 to 5 hours and a W_{50} value in the range of 10 to 33 hours.

The W_{50} parameter defines the width of the plasma profile at 50% Cmax, i.e. the duration over which the plasma concentrations are equal to or greater than 50% of the peak concentration. The parameter is determined by linear interpolation of the observed data and represents the difference in time between the first (or only) upslope crossing and the last (or only) downslope crossing in the plasma profile.

The in vitro release rates mentioned herein are, except where otherwise specified, those obtained by measurement using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37° C. and using UV detection at 270 nm.

The in viva absorption rate is determined from measurement of plasma concentration against time using the deconvolution techniqiue. A conventional release tramadol drop preparation (Tramal (trade mark), Grunenthal) was used as the weighting-function and the elimination half life of tramadol was taken as 7.8 hours.

The controlled release preparation according to the invention preferably contains an analgesically effective amount of tramadol or a pharmaceutically acceptable salt thereof, conveniently in the range of from 50 to 800 mg, especially 100, 200, 300, 400 to 600 mg (calculated as tramadol hydrochloride) per dosage unit.

The controlled release preparation according to the invention may be presented, for example, as granules, spheroids, pellets, multiparticulates, capsules, tablets, sachets, controlled release suspensions, or in any other suitable dosage form incorporating such granules, spheroids, pellets or multiparticulates.

The active ingredient in the preparation according to the invention may suitably be incorporated in a matrix. This may be any matrix that affords controlled release tramadol over at least a twelve hour period and preferably that affords in-vitro dissolution rates and in vivo absorption rates of tramadol within the ranges specified above. Preferably the matrix is a controlled release matrix. Alternatively, normal release matrices having a coating which provides for controlled release of the active ingredient may be used.

Suitable materials for inclusion in a controlled release matrix include

(a) Hydrophillic or hydrophobic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially alkylcelluloses are preferred. The preparation may conveniently contain between 1% and 80% (by weight) of one or more hydrophillic or hydrophobic polymers.

(b) Digestible, long chain (C_8–C_{50}, especially C_{12}–C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes. Hydrocarbons having a melting point of between 25 and 90° C. are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The preparation may conveniently contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(c) Polyalkylene glycols. The preparation may suitably contain up to 60% (by weight) of one or more polyalkylene glycols.

One particularly suitable controlled release matrix comprises one or more alkylcelluloses and one or more C_{12}–C_{36} aliphatic alcohols. The alkylcellulose is preferably C_1–C_6 alkyl cellulose, especially ethyl cellulose. The controlled release preparation according to the invention preferably contains from 1 to 20% (by weight), especially from 2 to 15% (by weight) of one or more alkylcelluloses.

The aliphatic alcohol may conveniently be lauryl alcohol, myristyl alcohol or stearyl alcohol but is preferably cetyl alcohol or more preferably cetostearyl alcohol. The controlled release preparation suitably contains from 5 to 30% (by weight) of aliphatic alcohol, especially from 10 to 25% (by weight) of aliphatic alcohol.

Optionally the controlled release matrix may also contain other pharmaceutically acceptable ingredients which are conventional in the pharmaceutical art such as diluents, lubricants, binders, granulating aids, colourants, flavourants, surfactants, pH adjusters, anti-adherents and glidants, e.g. dibutyl sebacate, ammonium hydroxide, oleic acid and colloidal silica.

The controlled release preparation according to the invention may conveniently be film coated using any film coating material conventional in the pharmaceutical art. Preferably an aqueous film coating is used.

Alternatively, the controlled release preparation according to the invention may comprise a normal release matrix having a controlled release coating. Preferably the preparation comprises film coated spheroids containing the active ingredient and a spheronising agent.

The spheronising agent may be any suitable pharmaceutically acceptable material which may be spheronised together with the active ingredient to form spheroids. A preferred spheronising agent is microcrystalline cellulose. The microcrystalline cellulose used may suitably be, for example, Avicel PII 101 or Avicel PII 102 (Trade Marks, FMC Corporation).

Optionally the spheroids may contain other pharmaceutically acceptable ingredients conventional in the pharmaceutical art such as binders, bulking agents and colourants. Suitable binders include water soluble polymers, water soluble hydroxyalkyl celluloses such as hydroxypropylcellulose or water insoluble polymers (which may also contribute controlled release properties) such as acrylic polymers or copolymers for example ethylcellulose. Suitable bulking agents include lactose.

The spheroids are coated with a material which permits release of the active ingredient at a controlled rate in an aqueous medium. Suitable controlled release coating materials include water insoluble waxes and polymers such as polymethacrylates (for example Eudragit polymers, Trade Mark) or water insoluble celluloses, particularly ethylcellulose. Optionally, water soluble polymers such as polyvinylpyrrolidone or water soluble celluloses such as hydroxypropylmethylcellulose or hydroxypropylcellulose may be included. Optionally other water soluble agents such as polysorbate 80 may be added.

Alternatively the drug may be coated onto inert non-pareil beads and the drug loaded beads coated with a material which permits control of the release of the active ingredient into the aqueous medium.

In a further aspect the present invention provides a process for preparing a controlled release preparation

according to the present invention comprising incorporating tramadol or a pharmaceutically acceptable salt thereof in a controlled release matrix, for example by

(a) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof and one or more alkylcelluloses,

(b) mixing the alkylcellulose containing granules with one or more C_{12-36} aliphatic alcohols; and optionally

(c) shaping and compressing the granules, and film coating, if desired; or

(d) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof, lactose and one or more alkylcelluloses with one or more C_{12-36} aliphatic alcohol; and, optionally,

(e) shaping and compressing the granules, and film coating, if desired.

The controlled release preparation according to the invention may also be prepared in the form of film coated spheroids by

(a) granulating the mixture comprising tramadol or a pharmaceutically acceptable salt thereof and a spheronising agent;

(b) extruding the granulated mixture to give an extrudate;

(c) spheronising the extrudate until spheroids are formed; and

(d) coating the spheroids with a film coat.

One preferred form of unit dose form in accordance with the invention comprises a capsule filled with controlled release particles essentially comprising the active ingredient, a hydrophobic fusible carrier or diluent and optionally a hydrophillic release modifier. In particular, the controlled release particles are preferably prepared by a process which comprises forming a mixture of dry active ingredient and fusible release control materials followed by mechanically working the mixture in a high speed mixer with an energy input sufficient to melt or soften the fusible material whereby it forms particles with the active ingredient. The resultant particles, after cooling, are suitably sieved to give particles having a size range from 0.1 to 3.0 mm, preferably 0.25 to 2.0 mm. An example according to the invention is described below which is suitable for the commercial production of dosage units.

When using such a processing technique it has been found that, in order most readily to achieve the desired release characteristics (both in vivo and in vitro as discussed above) the composition to be processed should comprises two essential ingredients namely:

(a) tramadol or salt thereof; and

(b) hydrophobic fusible carrier or diluent; optionally together with

(c) a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material.

We have found that the total amount of tramadol or pharmaceutically acceptable salt thereof in the composition may vary within wide limits, for example from 10 to 90% by weight thereof.

The hydrophobic fusible component (b) should be a hydrophobic material such as a natural or synthetic wax or oil, for example hydrogenated vegetable oil, hydrogenated castor oil, microcrystalline wax, Beeswax, Carnauba wax or glyceryl monostearate, and suitably has a melting point of from 35 to 140° C., preferably 45 to 110° C.

The release modifying component (c), when a water soluble fusible material, is conveniently a polyethylene glycol and, when a particulate material, is conveniently a pharmaceutically acceptable material such as dicalcium phosphate or lactose.

Another preferred process for the manufacture of a formulation in accordance with the invention comprises

(a) mechanically working in a high-speed mixer, a mixture of tramadol or a pharmaceutically acceptable salt in particulate form and a particulate, hydrophobic fusible carrier or diluent having a melting point from 35 to 140° C. and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates,

(b) breaking down the larger agglomerates to give controlled release seeds; and

(c) continuing mechanically working with optionally a further addition of low percentage of the carrier or diluent.

(d) optionally repeating steps (c) and possibly (b) one or more times.

This process is capable of giving a high yield (over 80%) of particles in a desired size range, with a desired uniformity of release rate of tramadol or salt thereof.

The resulting particles may be sieved to eliminate any over-or undersized material then formed into the desired dosage units by for example, encapsulation into hard gelatin capsules containing the required dose of the active substance or by compression into tablets.

In this method in accordance with the invention preferaby all the tramadol or salt thereof is added in step (a) together with a major portion of the hydrophobic fusible release control material used. Preferably the amount of fusible release control material added in step (a) is between 10% and 90% w/w of the total amount of ingredients added in the entire manufacturing operation, more preferably between 20% and 70% w/w.

Stage (a) of the process may be carried out in conventional high speed mixers with a standard stainless steel interior, e.g. a Collette Vactron 75 or equivalent mixer. The mixture is processed until a bed temperature about 40° C. or above is achieved and the resulting mixture acquires a cohesive granular texture, with particle sizes ranging from about 1–3 mm to fine powder in the case of non-aggregated original material. Such material, in the case of the embodiments described below, has the appearance of agglomerates which upon cooling below 40° C. have structural integrity and resistance to crushing between the fingers. At this stage the agglomerates are of an irregular size, shape and appearance.

The agglomerates are preferably allowed to cool. The temperature to which it cools is not critical and a temperature in the range room temperature to 37° C. may be conveniently used.

The agglomerates are broken down by any suitable means, which will comminute oversize agglomerates and produce a mixture of powder and small particles preferably with a diameter under 2 mm. It is currently preferred to carry out the classification using a Jackson Crockatt granulator using a suitable sized mesh, or a Comil with an appropriate sized screen. We have found that if too small a mesh size is used in the aforementioned apparatus the agglomerates melting under the action of the beater or impeller will clog the mesh and prevent further throughput of mixture, thus reducing yield. A mesh size of 12 has been found adequate.

The classified material is returned to the high speed mixer and processing continued. It is believed that this leads to cementation of the finer particles into particles of uniform size range.

In one preferred form of the method of the invention processing of the classified materials is continued, until the hydrophobic fusible materials used begin to soften/melt and optionally additional hydrophobic fusible material is then added. Mixing is continued until the mixture has been transformed into particles of the desired predetermined size range.

In order to ensure uniform energy input into the ingredients in the high speed mixer it is preferred to supply at least part of the energy by means of microwave energy.

Energy may also be delivered through other means such as by a heating jacket or via the mixer impeller and chopper blades.

After the particles have been formed they are cooled or allowed to cool, and may then be sieved to remove any over or undersized material.

The resulting particles may be used to prepare dosage units in accordance with the invention in the form of e.g. tablets or capsules in manners known per se.

We have also found that particles containing tramadol or a salt thereof produced by a melt processing as described in application PCT/SE93/00225 and the process described and claimed in our prior unpublished UK application No. 9324045.5 filed on 23 Nov. 1993 as well as the process described herein are particularly useful for processing into the form of tablets.

We have found that by suitable selection of the materials used in forming the particles and in the tabletting and the proportions in which they are used, enables a significant degree of control in the ultimate dissolution and release rates of the tramadol or salt thereof from the compressed tablets.

Usually, to form a tablet in accordance with the invention, particles prepared as described above will be admixed with tabletting excipients e.g. one or more of the standard excipients such as diluents, lubricants, binding agents, flow aids, disintegrating agents, surface active agents or water soluble polymeric materials.

Suitable diluents are e.g. microcrystalline cellulose, lactose and dicalcium phosphate. Suitable lubricants are e.g. magnesium stearate and sodium stearyl fumarate. Suitable binding agents are e.g. hydroxypropyl methyl cellulose, polyvidone and methyl cellulose.

Suitable disintegrating agents are starch, sodium starch glycolate, crospovidone and croscarmalose sodium.

Suitable surface active are Poloxamer 188®, polysorbate 80 and sodium lauryl sulfate.

Suitable flow aids are talc colloidal anhydrous silica.

Suitable water soluble polymers are PEG with molecular weights in the range 1000 to 6000.

To produce tablets in accordance with the invention, particles produced in accordance with the invention may be mixed or blended with the desired excipient(s), if any, using conventional procedures, e.g. using a Y-Cone or bin-blender and the resulting mixture compressed according to conventional tabletting procedure using a suitable size tabletting mould. Tablets can be produced using conventional tabletting machines, and in the embodiments described below were produced on standard single punch F3 Manesty machine or Kilian RLE15 rotary tablet machine.

Generally speaking we find that even with such a highly water soluble active agent as tramadol or salt thereof tablets formed by compression according to standard methods give very low release rates of the active ingredient e.g. corresponding to release over a period of greater than 24 hours, say more than 36. We have found that the release profile can be adjusted in a number of ways. For instance a higher loading of the drug will be associated with increased release rates; the use of larger proportions of the water soluble fusible material in the particles or surface active agent in the tabletting formulation will also be associated with a higher release rate of the active ingredient. By controlling the relative amounts of these ingredients it is possible to adjust the release profile of the tramadol or salt thereof.

In order that the invention may be well understood the following examples are given by way of illustration only.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention is further illustrated with the accompanying drawings in which:

FIG. **1** is a graphical depiction of the serum levels of tramadol following administration of one tablet according to Example 2 in 12 healthy volunteers; and

FIG. **2** is a graphical depiction of the plasma profile resulting from single dose administration of the tablet of Example 8 in comparison to the administration of a commercial preparation of tramadol drops 100 mg in a trial involving five healthy male volunteers.

EXAMPLE 1

Tablets having the following formulation were prepared:

	mg/tablet
Tramadol Hydrochloride	100
Lactose Ph. Eur.	68.0
Ethylcellulose (Surelease ® 25% solids)	15
Purified Water Ph. Eur.	13.3*
Cetostearyl Alcohol Ph. Eur. (Dehydag wax O)	42.00
Magnesium Stearate Ph. Eur.	2.00
Purified Talc Ph. Eur.	3.00
	230.00

*Removed during processing.

Tramadol hydrochloride (100 mg) and lactose (68 mg) were granulated, transferred to a fluid bed granulator and sprayed with ethylcellulose (15 mg) and water. The granules were then dried at 60° C. and passed through a 1 mm screen.

To the warmed tramadol containing granules was added molten cetostearyl alcohol (42 mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets.

The tablets were coated with a film coat having the formulation given below.

	mg/tablet
Hydropropylmethylcellulose Ph. Eur. 15 cps (Methocel E15)	0.770
Hydroxypropylmethylcellulose (Ph. Eur. 5 cps (Methocel E5)	3.87
Opaspray M-1-7111B (33% solids)	2.57
Polyethylene glycol 400 USNF	0.520

-continued

	mg/tablet
Purified Talc Ph. Eur.	0.270
Purified Water Ph. Eur.	55.52*

*Remove during processing.

EXAMPLE 2

Tablets having the following formulation were prepared:

	mg/tablet
Tramadol hydrochloride	100.0
Lactose Ph. Eur.	58.0
Ethylcellulose USNF (Ethocel 45 CP)	15.0
Cetostearyl alcohol Ph. Eur. (Dehydag wax O)	52.0
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

A mixture of tramadol hydrochloride (100 mg), lactose (58 mg) and ethylcellulose (15 mg) was granulated whilst adding molten cetostearyl alcohol (52 mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6 mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets which were coated with a film coat having the formulation given in Example 1.

EXAMPLE 3

Film coated tablets were produced following the procedure described in Example 2 and having the following formulation:

	mg/tablet
Tramadol hydrochloride	100.00
Lactose Ph. Eur.	70.50
Hydroxyethylcellulose Ph. Eur.	12.50
Cetostearyl alcohol Ph. Eur.	42.00
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

In Vitro Dissolution Studies

In vitro dissolution studies were conducted on tablets prepared as described above. Results are given in Table 1.

TABLE 1

	WT % TRAMADOL RELEASED		
Time (h)	Example 1	Example 2*	Example 3
1	39	35	43
2	52	47	60
4	67	62	84
8	82	78	97
12	90	86	—

*Measured on tablet core

In a trial involving 12 healthy volunteers the serum levels of tramadol following administration of one tablet according to Example 2 was found to be as illustrated in FIG. **1**.

EXAMPLES 4 AND 5

Particles having the formulations given in Table II below were prepared by the steps of:

i. Placing the ingredients (a) and (c) (total batch weight 0.7 kg) in the bowl of a liter capacity Collette Gral Mixer (or equivalent) equipped with variable speed mixing and granulating blades;

ii. Mixing the ingredients at about 150–1000 rpm whilst applying heat until the contents of the bowl are agglomerated.

iii. Classifying the agglomerated material by passage through a Comil and/or Jackson Crockatt to obtain controlled release seeds.

iv. Warming and mixing the classified material in the bowl of a 10 liter Collette Gral, until uniform multiparticulates of the desired pre-determined size range are formed in yield of greater than 80%. This takes approximately 5 minutes.

v. Discharging the multiparticulates from the mixer and sieving them to separate out the multiparticulates collected between 0.5 and 2 mm aperture sieves.

TABLE II

Example	4	5
(a) Tramadol HCl (Wt %)	50	75
(b) Hydrogenated Vegetable Oil (Wt %)	50	25

EXAMPLE 6

Samples of the particles from Example 4 were blended with magnesium stearate and purified talc using a Y-Cone or bin-blender. The blended mixture was then compressed using either (1) 14×6 mm, (2) 16×7 mm or (3) 18.6×7.5 mm capsule shaped tooling on a single punch F3 Manesty tabletting machine to give tablets giving 200, 300 and 400 mg of tramadol HCl. The ingredients per dosage unit amounted to the following:

TABLE III

TABLET	MG/TABLET		
INGREDIENT	1	2	3
Tramadol HCl	200	300	400
Hydrogenated Vegetable Oil	200	300	400
Sub Total	400	600	800
Purified Talc	12.63	18.95	25.26
Magnesium Searate	8.42	12.63	16.84

The tablets were assessed by the dissolution using Ph. Eur. Paddle Method 100 rpm, 0.1 N HCl.

To assess the non-compressed particles the Ph Eur. Paddle was replaced by a modified Ph Eur. Basket.

The results are shown in Table IV below;

TABLE IV

HOURS AFTER START OF TEST	Particles	Tablet 1	Tablet 2	Tablet 3
	% TRAMADOL HCl RELEASED			
1	54	16	15	15
2	68	23	20	21
3	76	28	25	25
4	82	32	28	28
6	89	40	35	35
8	93	46	41	40
10	96	50	45	45
12	98	55	49	49
16	100	63	57	56
20	NR	70	63	NR

These results confirm the effectiveness of the tabletting in reducing the release rate.

EXAMPLE 7

Samples of the particles from Example 5 were then tabletted using a procedure similar to Example 3 and the ingredients per unit dosage amounted to:

TABLE V

TABLET	MG/TABLET		
INGREDIENT	4	5	6
Tramadol HCl	200	300	400
Hydrogeziated Vegetable Oil	66.7	100	133
Sub Total	266.7	400	533
Purified Talc	7.63	11.44	15.25
Magnesium Stearate	5.16	7.63	10.17

The tablets and samples of non-compressed multiparticulates (each sample containing 400 mg of tramadol hydrochloride) were assessed by the dissolution method also described above. The results are shown in Table VI below;

TABLE VI

HOURS AFTER START OF TEST	Particles	Tablet 4	Tablet 5	Tablet 6
	% TRAMADOL HCl RELEASED			
1	77	43	40	42
2	92	64	55	56
3	98	75	65	66
4	100	83	72	73
6	102	94	83	84
8	102	100	91	91
10	102	NR	96	97

These results show that by increasing the loading of the highly water soluble tramadol hydrochloride (75% w/w in this example compared with 50% w/w in Example 6) a significantly faster release rate of the active ingredient can be achieved.

EXAMPLE 8

Example 4 was repeated but with the following formulation:

Tramadol HCl	200 mg/tablet
Hydrogenated Vegetable Oil	163.0 mg/tablet

The resulting multiparticulates were blended as described in Example 6 with the following;

Purified Talc	11.5 mg/tablet
Magnesium Stearate	7.66 mg/tablet

The blend was then compressed as described in Example 6 but using 15 mm×6.5 mm normal concave capsule shaped plain/plain punches.

The resulting tablets were then assessed by the dissolution method described above. The results are shown in Table V.

HOURS AFTER START OF TEST	% TRAMADOL HCl RELEASED
1	20
2	27
3	32
4	37
6	44
8	50
10	55
12	60
16	67
20	73
24	77

In a trial involving five healthy male volunteers the plasma profile resulting from single dose administrations of the above tablet are shown in FIG. **2** in comparison to the administration of a commercial preparation of Tramadol drops 100 mg.

What is claimed is:

1. A solid controlled release oral dosage form, comprising,

a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a normal release matrix,

said matrix overcoated with a controlled release coating comprising a polymethacrylate or a water insoluble cellulose,

said dosage form providing a therapeutic effect for at least about 24 hours.

2. The controlled release dosage form as claimed in claim **1**, wherein said controlled release coating comprises a polymethacrylate.

3. The controlled release dosage form as claimed in claim **1**, wherein said controlled release coating comprises a water insoluble cellulose.

4. The controlled release dosage form as claimed in claim **2**, wherein said controlled release coating further comprises a water soluble cellulose.

5. The controlled release dosage form as claimed in claim **3**, wherein said controlled release coating further comprises a polyvinylpyrrolidone.

6. The controlled release dosage form as claimed in claim **1**, containing from about 50 to 800 mg of tramadol or a pharmaceutically acceptable salt thereof, calculated as the hydrochloride salt.

7. The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37° C. and using UV detection at 270 nm, from about 0 to about 50% tramadol released after 1 hour; from about 0 to about 75% tramadol released after 2 hours; from about 10 to about 95% tramadol released after 4 hours; from about 35 to about 100% after 8 hours; from about 55 to about 100% tramadol released after 12 hours; from about 70 to about 100% tramadol released after 16 hours; and greater than 90% tramadol released after 24 hours, by weight.

8. The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37° C. and using UV detection at 270 nm, from about 0 to about 30% tramadol released after 1 hour; from about 0 to about 40% tramadol released after 2 hours; from about 3 to about 55% tramadol released after 4 hours; from about 10 to about 65% after 8 hours; from about 20 to about 75% tramadol released after 12 hours; from about 30 to about 88% tramadol released after 16 hours; from about 50 to about 100% tramadol released after 24 hours and greater than 80% tramadol released after 36 hours, by weight.

9. The controlled release dosage form as claimed in claim 1, having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37° C. and using UV detection at 270 nm, from about 15 to about 25% tramadol released after 1 hour; from about 25 to about 35% tramadol released after 2 hours; from about 30 to about 45% tramadol released after 4 hours; from about 40 to about 60% after 8 hours; from about 55 to about 70% tramadol released after 12 hours; and from about 60 to about 75% tramadol released after 16 hours, by weight.

10. The dosage form according to claim 1, which provides a t_{max} from about 3 to about 6 hours.

11. The dosage form according to claim 1, which provides a W_{50} from about 10 to about 33 hours.

12. The dosage form according to claim 3 wherein said water insoluble cellulose comprises ethylcellulose.

13. The dosage form of claim 1, comprising 100 mg tramadol hydrochloride.

14. The dosage form of claim 1, comprising 200 mg tramadol hydrochloride.

15. The dosage form of claim 1, comprising 300 mg tramadol hydrochloride.

16. The dosage form of claim 1, comprising 400 mg tramadol hydrochloride.

17. The dosage form of claim 1, comprising 600 mg tramadol hydrochloride.

* * * * *

RULE 7.1.1 CERTIFICATION

Counsel for Plaintiffs has consulted with counsel for Defendants who has advised that Defendants do not oppose the relief sought in the attached motion.

/s/ Jack B. Blumenfeld

Jack B. Blumenfeld (#1014)
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2164936

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA PRODUCTS L.P., NAPP PHARMACEUTICAL GROUP LTD., BIOVAIL LABORATORIES INTERNATIONAL, SRL, and ORTHO-MCNEIL, INC., Plaintiffs, v. PAR PHARMACEUTICAL, INC. and PAR PHARMACEUTICAL COMPANIES, INC., Defendants.	)	C.A. No. 07-255 (JJF) (CONSOLIDATED)

ORDER GRANTING UNOPPOSED MOTION FOR LEAVE TO AMEND COMPLAINT

Having considered plaintiffs' unopposed motion for leave to amend their complaint.

IT IS HEREBY ORDERED that:

Plaintiffs' Unopposed Motion for Leave to Amend Complaint is GRANTED.

Date: _____

_____
UNITED STATES DISTRICT JUDGE

2164934

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA PRODUCTS L.P., NAPP PHARMACEUTICAL GROUP LTD., BIOVAIL LABORATORIES INTERNATIONAL, SRL, and ORTHO-MCNEIL, INC.,	)	
Plaintiffs,	)	C.A. No. 07-255 (JJF) (CONSOLIDATED)
v.	)	
PAR PHARMACEUTICAL, INC. and PAR PHARMACEUTICAL COMPANIES, INC.,	)	
Defendants.	)	

UNOPPOSED MOTION FOR LEAVE TO AMEND COMPLAINT

Plaintiffs move, pursuant to Fed. R. Civ. P. 15(a) and D. Del. LR 15.1, to amend their complaint in this action in order to allege a second claim for declaratory judgment relief based on the real and imminent threat of Par's infringement of United States Patent No. 7,074,430 ("the '430 patent"). The grounds for this motion are that the Court should freely give leave when justice so requires and that the proposed amended complaint meets the factors considered by courts. Defendants do not oppose this motion. A copy of the Amended Complaint is attached as Exhibit 1, and a redlined version is attached as Exhibit 2. A form of order granting this motion is also attached hereto.

INTRODUCTION

The three complaints in this action allege infringement of Purdue's and Napp's U.S. Patent No. 6,254,887 ("the '887 patent") based on Par's filing of an Abbreviated New Drug Application ("ANDA") for FDA approval to manufacture and sell a generic copy of ULTRAM® ER, a controlled-release formulation of the analgesic tramadol. The '430 patent, which plaintiffs seek to add, is a continuation of the '887 patent.

Plaintiffs timely commenced suit for infringement of the '887 patent in response to Par's "Paragraph IV" notice pursuant to 21 U.S.C. § 355(j)(2)(B)(ii), contending that Par's proposed generic would not infringe the '887 patent, which is listed in the FDA "Orange Book" as relating to ULTRAM® ER. Plaintiffs timely filed two subsequent suits in response to later notices by Par relating to different dosage strengths of the same formulation. The three complaints are identical, except for the dates of the Paragraph IV letters and the different dosage strengths referenced. During discovery, Par produced documents indicating that its proposed controlled-release tramadol formulation, if approved, would also infringe the '430 patent. The '430 patent, however, is not listed in the Orange Book and, under the controlling authorities, cannot be the subject of a patent infringement suit based on the filing of Par's ANDA alone. *See, e.g., Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1325-26 (Fed. Cir. 2003).

Nevertheless, Par's prosecution of its ANDA application and, on information and belief, its preparation to make, sell and offer for sale its generic copy of ULTRAM® ER creates a controversy of sufficient immediacy and reality to create jurisdiction for a declaratory judgment claim under the Supreme Court's 2007 decision in *MedImmune, Inc. v. Genentech, Inc.*, 127 S. Ct. 764, 771 (2007).

ARGUMENT

A. The Controlling Legal Standard

Federal Rule of Civil Procedure 15(a) provides that a party may amend a pleading by leave of court, and "[t]he court should freely give leave when justice so requires." Consistent with the Supreme Court standard stated in *Foman*, the Third Circuit applies a four-factor test to determine when an amendment should be allowed. The proposed amendment fully meets that standard.

B. Plaintiffs Have Not Unduly Delayed and Have Acted in Good Faith in Proposing to Add a Claim for the '430 Patent

Plaintiffs filed the three complaints in this case in response to each of Par's three "Paragraph IV" notices alleging that the '887 patent, the only patent listed in the FDA's Orange Book as covering the drug ULTRAM® ER, is invalid and/or will not be infringed by the commercial manufacture, use, or sale of Par's products. Based on an analysis of documents provided in discovery, including Par's ANDA, plaintiffs now have a good-faith basis to believe that Par's proposed product threatens to infringe the '430 patent. Although, to plaintiffs' knowledge, Par has not received a tentative approval of its ANDA from the FDA, the deadline to amend the pleadings under the Scheduling Order is March 21, 2008. Plaintiffs have thus acted in good faith and have not unduly delayed in moving to amend the complaint to add a declaratory judgment claim of threatened infringement of the '430 patent to this case.

C. Plaintiffs' Amended Complaint Will Not Prejudice Par

There is no prejudice to Par in allowing plaintiffs' proposed amendment. No additional document discovery would be required if the '430 patent were added to the current action. Purdue has already provided documentary discovery relating to the prosecution of the '430 patent application, including production of the prosecution files from Purdue and from its outside prosecution counsel. The inventors of the '430 patent, all of whom reside overseas, are the same as the inventors of the '887 patent, and none of them has yet been deposed. The only witness Par has deposed to date is the prosecuting attorney, who already testified as a 30(b)(6) witness on behalf of his firm on the prosecution of the '430 patent.

The addition of the '430 patent to the current suit would serve the interest of judicial economy and conserve the resources of the Court and the parties. The issue of infringement of both patents, which are closely related, can be litigated in a single proceeding

without altering the schedule. The alternative, to put off litigation of the '430 patent until after Par receives tentative FDA approval for its tramadol formulation, would be far more prejudicial to Par, as it would require a separate suit at a later date, which would increase the costs to Par, to plaintiffs, and to the Courts.

D. Plaintiffs' Proposed Amendment Is Not Futile

An amendment is not futile for purposes of a motion to amend a complaint unless "the complaint, as amended, would fail to state a claim upon which relief could be granted." *Shane v. Fauver*, 213 F.3d, 113, 115 (3d Cir. 2000). Plaintiffs' proposed amendment satisfies this standard.

With respect to jurisdiction, declaratory judgment jurisdiction requires that under all the facts and circumstances, there is a substantial controversy between parties with adverse legal interests and that the controversy is sufficiently immediate and real. *MedImmune*, 127 S. Ct. at 771. Here, the controversy is both immediate and real. Par has submitted its ANDA, which is currently being processed by the FDA. Upon receipt of tentative approval by the FDA, Par will be able to make and sell its generic copy of ULTRAM® ER if it prevails against plaintiffs' claims relating to the '887 patent or if the 30-month stay expires during the pendency of any appeal. On information and belief, Par has taken steps to plan for the manufacture and sale of its generic at the earliest possible date.

Apposite here is *Teva Pharms. USA, Inc. v. Novartis Pharms. Corp.*, 482 F.3d. 1330 (Fed. Cir. 2007). There, the patent owner (Novartis) commenced suit against a proposed generic (Teva) asserting infringement of one patent listed in the Orange Book, but not asserting four other patents. Teva, the ANDA-filer, sought declaratory judgment that the remaining four patents were invalid or not infringed. *Id.* at 1334-35. The District Court dismissed the

declaratory judgment claim for lack of jurisdiction applying the Federal Circuit's pre-*MedImmune* requirement of showing of imminent threat of suit. The Federal Circuit reversed, relying on the Supreme Court's decision in *MedImmune*. The Court concluded that allowing the declaratory judgment jurisdiction action to proceed "is consistent with the 'controversy' requirement in Article III and the Declaratory Judgment Act because the suit will achieve a final determination that resolves the entire dispute between Teva and Novartis." *Id.* at 1346.

The facts surrounding this controversy support both jurisdiction and sufficiency on the merits for purposes of Rule 15(a). Plaintiffs' proposed amendment is based on the same facts that underlie the existing claim of infringement of the '887 patent. Analysis and adjudication of this infringement claim will depend on the facts relating to Par's proposed formulation, including, *inter alia*, the composition of the proposed formulation. These same facts will likewise determine whether Par's proposed formulation threatens infringement of the '430 patent, a continuation of the '887 patent.

Moreover, in light of the existing '887 infringement claims, there can be no doubt that a substantial controversy between parties with adverse legal interests already exists on these facts, and that the controversy is immediate and real. On information and belief, Par's actions toward bringing its generic formulation of ULTRAM® ER to the market creates the threat of infringement of the '430 patent once Par receives tentative FDA approval. Accordingly, "the facts alleged, under all the circumstances, show that there is a substantial controversy, between

parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." *MedImmune*, 127 S. Ct. at 771.[1]

CONCLUSION

For the foregoing reasons, plaintiffs' unopposed motion should be granted.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

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[1] In the course of consulting with Par to obtain Par's consent to the amended complaint, with respect to the claim of "exceptional case" under 35 U.S.C. § 285 (paragraph 27 of the Amended Complaint), plaintiffs made clear that this amended complaint is without any prejudice to plaintiffs' right to assert any bases for exceptional case under the controlling authorities. Specifically, should those authorities allow plaintiffs to rely on willful infringement of the '430 patent as a basis for exceptional case to any extent, plaintiffs stated that they reserve their right to do so. Par noted its objection to any extent plaintiffs rely on willful infringement as a basis for exceptional case prior to an occurrence of actual infringement. This disagreement between the parties does not preclude plaintiffs' proposed amendment, to which Par has consented; it is an issue for another day.

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March 21, 2008
2164912

EXHIBIT 1

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA PRODUCTS L.P., NAPP PHARMACEUTICAL GROUP LTD., BIOVAIL LABORATORIES INTERNATIONAL, SRL, and ORTHO-MCNEIL, INC.,	)	
Plaintiffs,	)	C.A. No. 07-255 (JJF) (CONSOLIDATED)
v.	)	
PAR PHARMACEUTICAL, INC. and PAR PHARMACEUTICAL COMPANIES, INC.,	)	
Defendants.	)	

AMENDED COMPLAINT

Plaintiffs Purdue Pharma Products L.P., Napp Pharmaceuticals Group Ltd., Biovail Laboratories International, SRL, and Ortho-McNeil, Inc., for their Amended Complaint herein, aver as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code.

JURISDICTION AND VENUE

2. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202.

3. Venue is proper in this Judicial District under 28 U.S.C. §§ 1391(b) and (c) and § 1400(b).

THE PARTIES

4. Plaintiff Purdue Pharma Products L.P. ("Purdue") is a limited partnership organized and existing under the laws of the State of Delaware, having a place of business at One

Stamford Forum, 201 Tresser Boulevard, Stamford, Connecticut 06901-3431. Purdue is an owner by assignment of the patents in suit identified in paragraphs 10 and 11 below.

5. Plaintiff Napp Pharmaceutical Group Ltd. ("Napp") is a private limited company organized and existing under the laws of the United Kingdom, having a place of business at Cambridge Science Park, Milton Road, Cambridge, CB4 0GW. Napp is an owner by assignment of the patents in suit identified in paragraphs 10 and 11 below.

6. Plaintiff Biovail Laboratories International, SRL ("Biovail") is a corporation organized and existing under the laws of Barbados, having a place of business in Carolina, Puerto Rico. Biovail is the holder of New Drug Application ("NDA") No. 21-692 and manufactures the controlled-release tramadol hydrochloride pain relief medication Ultram® ER.

7. Plaintiff Ortho-McNeil, Inc. ("Ortho-McNeil") is a corporation organized and existing under the laws of the State of New Jersey, having a place of business at 1000 Route 202 South, Raritan, New Jersey 08869. Ortho-McNeil is a licensee of the '887 patent in suit identified in paragraph 10 below, and markets and distributes Ultram® ER in the United States.

8. Upon information and belief, defendant Par Pharmaceutical, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at One Ram Ridge Road, Spring Valley, New York 10977.

9. Upon information and belief, defendant Par Pharmaceutical Companies, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 300 Tice Boulevard, Woodcliff Lake, New Jersey 07677. Upon information and belief, Par Pharmaceutical Companies, Inc. is the parent corporation of Par Pharmaceutical, Inc., and Par Pharmaceutical, Inc. is a wholly-owned subsidiary of Par Pharmaceutical Companies, Inc.

THE PATENTS IN SUIT

10. Purdue and Napp are the lawful owners of all right, title and interest in and to the following United States patent, including all right to sue and to recover for past infringement thereof, which patent is listed in the U.S. Food and Drug Administration's ("FDA") "Orange Book" (*Approved Drug Products With Therapeutic Equivalence Evaluation*) as covering Ultram® ER:

United States Patent No. 6,254,887, entitled "CONTROLLED RELEASE TRAMADOL" ("the '887 patent"), a copy of which is attached hereto as Exhibit A, which was duly and legally issued on July 3, 2001, naming Ronald Brown Miller, Stuart Thomas Leslie, Sandra Therese Antoinette Malkowska, Kevin John Smith, Walter Wimmer, Horst Winkler, Udo Hahn, and Derek Allan Prater as the inventors.

11. Purdue and Napp are also the lawful owners of all right, title and interest in and to the following United States patent, including all right to sue and to recover for past infringement thereof:

United States Patent No. 7,074,430, entitled "CONTROLLED RELEASE TRAMADOL TRAMADOL [sic] FORMULATION" ("the '430 patent"), a copy of which is attached hereto as Exhibit B, which was duly and legally issued on July 11, 2006, naming Ronald Brown Miller, Sandra Therese Antoinette Malkowska, Walter Wimmer, Udo Hahn, Stuart Thomas Leslie, Kevin John Smith, Horst Winkler, and Derek Allan Prater as the inventors.

PAR'S ANDA

12. Upon information and belief, Par's Abbreviated New Drug Application ("ANDA"), submitted to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), seeks approval to engage in the commercial manufacture, use, and sale of

Tramadol Hydrochloride Extended Release Tablets, 100 mg, 200 mg, and 300 mg ("Par's Tablets"), a generic version of Biovail's Ultram® ER, before the expiration of the '887 patent.

13. Upon information and belief, Par's ANDA contains a "Paragraph IV" certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging that the '887 patent, listed in the FDA's Orange Book as a patent covering the drug Ultram® ER, is invalid and/or will not be infringed by the commercial manufacture, use or sale of Par's Tablets.

14. In a letter dated March 27, 2007 addressed to Biovail and Euroceltique, S.A. (listed as the assignee on the face of the '887 patent and an entity associated with Purdue and Napp), Par provided "notice" with respect to its 200 mg Tablets and the '887 patent under 21 U.S.C. § 355(j)(2)(B)(ii) ("Par's 1st notice").

15. On May 9, 2007, within the 45-day period provided by statute, Plaintiffs filed a complaint in this Court for patent infringement with respect to Par's 200 mg Tablets. This complaint received Civil Action No. 07-255-JJF.

16. In a letter dated May 21, 2007 addressed to Biovail, Napp, and Purdue, Par provided "notice" with respect to its 100 mg and 200 mg Tablets and the '887 patent under 21 U.S.C. § 355(j)(2)(B)(ii) ("Par's 2nd notice").

17. On June 28, 2007, within the 45-day period provided by statute, Plaintiffs filed a complaint in this Court for patent infringement with respect to Par's 100 and 200 mg Tablets. This complaint received Civil Action No. 07-414-JJF.

18. In a letter dated September 24, 2007 addressed to Biovail, Napp, and Purdue, Par provided "notice" with respect to its 300 mg Tablets and the '887 patent under 21 U.S.C. § 355(j)(2)(B)(ii) ("Par's 3rd notice").

19. On October 24, 2007, within the 45-day period provided by statute, Plaintiffs filed a complaint in this Court for patent infringement with respect to Par's 300 mg Tablets. This complaint received Civil Action No. 07-666-JJF.

20. Par's 1st, 2nd, and 3rd notices do not provide any valid basis for concluding that the '887 patent is invalid and/or not infringed by its Tablets.

FIRST CLAIM FOR RELIEF:
PATENT INFRINGEMENT UNDER 35 U.S.C. § 271(e)(2)

21. Par's submission of its ANDA was an act of infringement of the '887 patent under the United States Patent Law, 35 U.S.C. § 271(e)(2)(A).

22. Upon information and belief, the composition of Par's Tablets is covered by one or more claims of the '887 patent.

23. Upon information and belief, Par's commercial manufacture, use, sale, and/or offer for sale of its Tablets would infringe, contribute to the infringement of, and induce the infringement of one or more claims of the '887 patent.

24. Upon information and belief, Par has been aware of the existence of the '887 patent, and has no reasonable basis for believing that its Tablets will not infringe the '887 patent, thus rendering the case "exceptional," as that term is used in 35 U.S.C. § 285.

25. The acts of infringement by Par set forth above will cause plaintiffs irreparable harm for which they have no adequate remedy at law, and will continue unless enjoined by this Court.

SECOND CLAIM FOR RELIEF: DECLARATORY JUDGMENT OF PATENT INFRINGEMENT

26. Upon information and belief, once the FDA grants tentative approval of Par's ANDA, Par will undertake substantial activities directed toward engaging in infringement, contributory infringement, and active inducement of infringement of the '430 patent by making,

using and undertaking substantial preparations for offering to sell, without authority from plaintiffs, its Tablets, whose compositions are covered by one or more claims of the '430 patent.

27. Upon information and belief, Par has been aware of the existence of the '430 patent but, once the FDA grants tentative approval of Par's ANDA, Par will nevertheless engage in substantial activities directed toward infringing, contributorily infringing, and actively inducing the infringement of the '430 patent. These activities will be in total disregard for plaintiffs' lawful rights under the '430 patent, thus rendering this case "exceptional" as that term is set forth in 35 U.S.C. § 285.

28. Once the FDA grants tentative approval of Par's ANDA, these substantial activities engaged in by Par directed toward infringement, contributory infringement, and active inducement of infringement as set forth above demonstrate the existence of an actual and justiciable controversy, and, if allowed to continue and progress, will inevitably constitute infringement, contributory infringement, and active inducement of infringement of the '430 patent, will cause plaintiffs irreparable harm for which they have no adequate remedy at law, and will continue unless preliminarily and permanently enjoined by this Court.

WHEREFORE, plaintiffs pray for judgment:

On the First Claim for Relief:

A. Adjudging that Par Pharmaceutical Companies, Inc. and Par Pharmaceutical, Inc. have infringed the '887 patent, and that the commercial sale, offer for sale, and/or manufacture of Par's Tablets would infringe, induce infringement of, and/or contribute to the infringement of the '887 patent;

B. Adjudging, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Par's ANDA No. 78-783, under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), to be a date not earlier than the date of expiration of the '887 patent;

C. Preliminarily and permanently enjoining, pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283 and Rule 65, Fed. R. Civ. P., Par Pharmaceutical Companies, Inc. and Par Pharmaceutical, Inc., their officers, agents, servants, employees, parents, subsidiaries, divisions, affiliate corporations, other related business entities, and all other persons acting in concert, participation or in privity with them, and their successors and assigns, from any commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product that infringes the '887 patent;

D. Declaring this an exceptional case and awarding plaintiffs their attorneys' fees, as provided by 35 U.S.C. §§ 271(e)(4) and 285; and

E. Awarding plaintiffs such other and further relief as this Court may deem just and proper.

On the Second Claim for Relief:

F. Declaring that the manufacture, use, and substantial preparations for offering for sale of Par's Tablets, if allowed to continue and progress, will constitute infringement, contributory infringement and active inducement of infringement of the '430 patent;

G. Preliminarily and permanently enjoining, pursuant to 35 U.S.C. § 283 and Rule 65, Fed. R. Civ. P., Par Pharmaceutical Companies, Inc. and Par Pharmaceutical, Inc., their officers, agents, servants, employees, parents, subsidiaries, divisions, affiliate corporations, other related business entities, and all other persons acting in concert, participation or in privity with them, and their successors and assigns, from any commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product that infringes the '430 patent;

H. Declaring this an exceptional case and awarding plaintiffs their attorneys' fees, as provided by 35 U.S.C. § 285; and

I. Awarding plaintiffs such other and further relief as this Court may deem just and proper.

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March 21, 2008
2164941

EXHIBIT 2

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PURDUE PHARMA PRODUCTS L.P., NAPP PHARMACEUTICAL GROUP LTD., BIOVAIL LABORATORIES INTERNATIONAL, SRL, and ORTHO-MCNEIL, INC., Plaintiffs, v. PAR PHARMACEUTICAL, INC. and PAR PHARMACEUTICAL COMPANIES, INC., Defendants.	C.A. No. _____ 07-255 (JJF) (CONSOLIDATED)

AMENDED COMPLAINT

Plaintiffs Purdue Pharma Products L.P., Napp Pharmaceuticals Group Ltd., Biovail Laboratories International, SRL, and Ortho-McNeil, Inc., for their Amended Complaint herein, aver as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code.

JURISDICTION AND VENUE

2. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201 and ~~2201.~~2202.

3. Venue is proper in this Judicial District under 28 U.S.C. §§ 1391(b) and (c) and § 1400(b).

THE PARTIES

4. Plaintiff Purdue Pharma Products L.P. ("Purdue") is a limited partnership organized and existing under the laws of the State of Delaware, having a place of business at One Stamford Forum, 201 Tresser Boulevard, Stamford, Connecticut 06901-3431. Purdue is an owner by assignment of the ~~patent~~patents in suit identified in ~~paragraph~~paragraphs 10 and 11 below.

5. Plaintiff Napp Pharmaceutical Group Ltd. ("Napp") is a private limited company organized and existing under the laws of the United Kingdom, having a place of business at Cambridge Science Park, Milton Road, Cambridge, CB4 0GW. Napp is an owner by assignment of the ~~patent~~patents in suit identified in ~~paragraph~~paragraphs 10 and 11 below.

6. Plaintiff Biovail Laboratories International, SRL ("Biovail") is a corporation organized and existing under the laws of Barbados, having a place of business in Carolina, Puerto Rico. Biovail is the holder of New Drug Application ("NDA") No. 21-692 and manufactures the controlled-release tramadol hydrochloride pain relief medication Ultram® ER.

7. Plaintiff Ortho-McNeil, Inc. ("Ortho-McNeil") is a corporation organized and existing under the laws of the State of New Jersey, having a place of business at 1000 Route 202 South, Raritan, New Jersey 08869. Ortho-McNeil is a licensee of the '887 patent in suit identified in paragraph 10 below, and markets and distributes Ultram® ER in the United States.

8. Upon information and belief, defendant Par Pharmaceutical, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at One Ram Ridge Road, Spring Valley, New York 10977.

9. Upon information and belief, defendant Par Pharmaceutical Companies, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 300 Tice Boulevard, Woodcliff Lake, New Jersey 07677. Upon information and belief, Par Pharmaceutical Companies, Inc. is the parent corporation of Par Pharmaceutical, Inc., and Par Pharmaceutical, Inc. is a wholly-owned subsidiary of Par Pharmaceutical Companies, Inc.

THE ~~PATENT~~PATENTS IN SUIT

10. Purdue and Napp are the lawful owners of all right, title and interest in and to the following United States patent, including all right to sue and to recover for past infringement thereof, which patent is listed in the U.S. Food and Drug Administration's ("FDA") "Orange Book" (*Approved Drug Products With Therapeutic Equivalence Evaluation*) as covering Ultram® ER:

United States Patent No. 6,254,887, entitled "CONTROLLED RELEASE TRAMADOL" ("the '887 patent"), a copy of which is attached hereto as Exhibit A, which was duly and legally issued on July 3, 2001, naming Ronald Brown Miller, Stuart Thomas Leslie, Sandra Therese Antoinette Malkowska, Kevin John Smith, Walter Wimmer, Horst Winkler, Udo Hahn, and Derek Allan Prater as the inventors.

11. Purdue and Napp are also the lawful owners of all right, title and interest in and to the following United States patent, including all right to sue and to recover for past infringement thereof:

United States Patent No. 7,074,430, entitled "CONTROLLED RELEASE TRAMADOL TRAMADOL [sic] FORMULATION" ("the '430 patent"), a copy of which is attached hereto as Exhibit B, which was duly and legally issued on July 11, 2006, naming Ronald Brown Miller, Sandra Therese Antoinette Malkowska, Walter Wimmer, Udo Hahn,

Stuart Thomas Leslie, Kevin John Smith, Horst Winkler, and Derek Allan Prater as the inventors.

PAR'S ANDA

12. ~~11.~~ Upon information and belief, Par ~~submitted an~~'s Abbreviated New Drug Application ("ANDA"), submitted to the FDA~~,~~ under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), ~~seeking~~seeks approval to engage in the commercial manufacture, use, and sale of Tramadol Hydrochloride Extended Release Tablets, 100 mg, 200 mg, and 300 mg ("Par's Tablets"), a generic version of Biovail's Ultram® ER, before the expiration of the '887 patent.

13. ~~12.~~ Upon information and belief, Par's ANDA contains a "Paragraph IV" certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV)~~,~~ alleging that the '887 patent, listed in the FDA's Orange Book as a patent covering the drug Ultram® ER, is invalid and/or will not be infringed by the commercial manufacture, use or sale of Par's Tablets.

14. ~~13.~~ In a letter dated March 27, 2007 addressed to Biovail and Euroceltique, S.A. (~~"Euroceltique" is~~ listed as the assignee on the face of the '887 patent and ~~is~~ an entity associated with Purdue and Napp), Par ~~sent~~provided "notice" with respect to its 200 mg Tablets and the '887 patent under 21 U.S.C. § 355(j)(2)(B)(ii) ("Par's 1st notice").

15. On May 9, 2007, within the 45-day period provided by statute, Plaintiffs filed a complaint in this Court for patent infringement with respect to Par's 200 mg Tablets. This complaint received Civil Action No. 07-255-JJF.

16. In a letter dated May 21, 2007 addressed to Biovail, Napp, and Purdue, Par provided "notice" with respect to its 100 mg and 200 mg Tablets and the '887 patent under 21 U.S.C. § 355(j)(2)(B)(ii) ("Par's 2nd notice").

17. On June 28, 2007, within the 45-day period provided by statute, Plaintiffs filed a complaint in this Court for patent infringement with respect to Par's 100 and 200 mg Tablets. This complaint received Civil Action No. 07-414-JJF.

18. In a letter dated September 24, 2007 addressed to Biovail, Napp, and Purdue, Par provided "notice" with respect to its 300 mg Tablets and the '887 patent under 21 U.S.C. § 355(j)(2)(B)(ii) ("Par's 3rd notice").

19. On October 24, 2007, within the 45-day period provided by statute, Plaintiffs filed a complaint in this Court for patent infringement with respect to Par's 300 mg Tablets. This complaint received Civil Action No. 07-666-JJF.

20. ~~14.~~ Par's ~~notice does~~ 1st, 2nd, and 3rd notices do not provide any valid basis for concluding that the '887 patent is invalid and/or not infringed~~.~~ by its Tablets.

~~15. Upon information and belief, the composition of Par's Tablets are covered by one or more claims of the '887 patent.~~

FIRST CLAIM FOR RELIEF:
PATENT INFRINGEMENT UNDER 35 U.S.C. § 271(e)(2)

21. ~~16.~~ Par's submission of its ANDA was an act of infringement of the '887 patent under the United States Patent Law, 35 U.S.C. § 271(e)(2)(A).

22. Upon information and belief, the composition of Par's Tablets is covered by one or more claims of the '887 patent.

23. ~~17.~~ Upon information and belief, Par's commercial manufacture, use, sale, and/or offer for sale of its Tablets would infringe, contribute to the infringement of, and induce the infringement of one or more claims of the '887 patent.

24. ~~18.~~ Upon information and belief, Par has been aware of the existence of the '887 patent, and has no reasonable basis for believing that ~~Par's~~its Tablets will not infringe the '887 patent, thus rendering the case "exceptional," as that term is used in 35 U.S.C. § 285.

25. ~~19.~~ The acts of infringement by Par set forth above will cause plaintiffs irreparable harm for which they have no adequate remedy at law, and will continue unless enjoined by this Court.

SECOND CLAIM FOR RELIEF: DECLARATORY JUDGMENT OF PATENT INFRINGEMENT

26. Upon information and belief, once the FDA grants tentative approval of Par's ANDA, Par will undertake substantial activities directed toward engaging in infringement, contributory infringement, and active inducement of infringement of the '430 patent by making, using and undertaking substantial preparations for offering to sell, without authority from plaintiffs, its Tablets, whose compositions are covered by one or more claims of the '430 patent.

27. Upon information and belief, Par has been aware of the existence of the '430 patent but, once the FDA grants tentative approval of Par's ANDA, Par will nevertheless engage in substantial activities directed toward infringing, contributorily infringing, and actively inducing the infringement of the '430 patent. These activities will be in total disregard for plaintiffs' lawful rights under the '430 patent, thus rendering this case "exceptional" as that term is set forth in 35 U.S.C. § 285.

28. Once the FDA grants tentative approval of Par's ANDA, these substantial activities engaged in by Par directed toward infringement, contributory infringement, and active inducement of infringement as set forth above demonstrate the existence of an actual and justiciable controversy, and, if allowed to continue and progress, will inevitably constitute infringement, contributory infringement, and active inducement of infringement of the '430

patent, will cause plaintiffs irreparable harm for which they have no adequate remedy at law, and will continue unless preliminarily and permanently enjoined by this Court.

WHEREFORE, plaintiffs pray for judgment:

On the First Claim for Relief:

A. Adjudging that Par Pharmaceutical Companies, Inc. and Par Pharmaceutical, Inc. have infringed the '887 patent, and that the commercial sale, offer for sale, and/or manufacture of Par's Tablets would infringe, induce infringement of, and/or contribute to the infringement of the '887 patent;

B. Adjudging, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Par's ANDA ~~for Tramadol Hydrochloride Extended Release Tablets, 200 mg,~~No. 78-783, under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)), to be a date not earlier than the date of expiration of the '887 patent;

C. Preliminarily and permanently enjoining, pursuant to 35 U.S.C. §§ 271(e)(4)(B) and 283 and Rule 65, Fed. R. Civ. P., Par Pharmaceutical Companies, Inc. and Par Pharmaceutical, Inc., their officers, agents, servants, employees, parents, subsidiaries, divisions, affiliate corporations, other related business entities, and all other persons acting in concert, participation or in privity with them, and their successors and assigns, from any commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product that infringes the '887 patent;

D. Declaring this an exceptional case and awarding plaintiffs their attorneys' fees, as provided by 35 U.S.C. §§ 271(e)(4) and 285; and

E. Awarding plaintiffs such other and further relief as this Court may deem just and proper.

On the Second Claim for Relief:

A. Declaring that the manufacture, use, and substantial preparations for offering for sale of Par's Tablets, if allowed to continue and progress, will constitute infringement, contributory infringement and active inducement of infringement of the '430 patent;

B. Preliminarily and permanently enjoining, pursuant to 35 U.S.C. § 283 and Rule 65, Fed. R. Civ. P., Par Pharmaceutical Companies, Inc. and Par Pharmaceutical, Inc., their officers, agents, servants, employees, parents, subsidiaries, divisions, affiliate corporations, other related business entities, and all other persons acting in concert, participation or in privity with them, and their successors and assigns, from any commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any drug product that infringes the '430 patent;

C. Declaring this an exceptional case and awarding plaintiffs their attorneys' fees, as provided by 35 U.S.C. § 285; and

D. Awarding plaintiffs such other and further relief as this Court may deem just and proper.

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